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14. ABSTRACT

A large and under-recognized sub-set of patients suffer from both traumatic brain injury (TBI) and alcohol abuse/dependence (AA/D). This group appears to use alcohol to self-treat fronto-limbic disinhibition, expressed clinically as affective lability, following TBI. This often results in AA/D and worsens TBI prognosis. The primary study hypothesis states that symptom frequencies of fronto-limbic disinhibition, expressed as affective lability, will decrease significantly in TBI subjects treated with divalproex sodium, a mood stabilizing medication, as compared to placebo. To test the primary hypothesis, we propose an 8 week, double-blind, randomized, controlled trial comparing divalproex sodium to placebo in 50 subjects—25 per group--who suffer from both TBI and AA/D. Subjects will be recruited through the initiating site located at the Department of Veterans Affairs Medical Center, Denver. Final approval from multiple review bodies was granted on September 15, 2009. Active subject recruitment and all subject follow-up is complete. There are only very preliminary results to report at this time.

15. SUBJECT TERMS

Traumatic Brain Injury, Alcohol Use, Mood, Mood Stabilization

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Introduction

Traumatic brain injury (TBI) is highly prevalent in at risk occupations including US service personnel. Of particular concern now are those wounded in combat in Iraq and Afghanistan where TBI appears to account for a larger proportion of casualties than in prior U.S. wars. Reports from Operation Iraqi Freedom (OIF) suggest that as many as one-quarter of personnel injured in combat there suffer TBI. (Okie, 2005) Psychiatric and neurocognitive disorders—especially disorders of mood--have been noted in as many as three-quarters of combatants who suffered TBI in previous conflicts (Lishman, 1973) and are often more adversely affected by emotional problems than by physical disabilities. (Nelson et al., 1998) Although specific data are not at hand, published frequencies suggest that as many as one combat related case of TBI in every five may likely exhibit symptoms related to fronto-limbic disinhibition that is expressed as a poorly controlled, or labile, affect. It is that condition that caught our clinical interest and led to a preliminary research project.

Specifically, the Principal Investigator (PI) observed a clinical population of former service personnel who served in high risk environments such as paratroop units, flight crews, and below decks aboard ship and who had suffered TBI. Common to all was a poorly managed affective irritability or anxiety that began after TBI and was often misdiagnosed as another Axis I psychiatric disorder, usually a mood disorder such as bipolar illness, or schizoaffective illness. Likewise, all of the cases had no such symptoms prior to TBI. This posed a clinical question: How to treat post-TBI affective lability/ fronto-limbic disinhibition?

As a class of agents, anticonvulsant medication appears, empirically, to lessen the affective lability in TBI. Carbamazepine may ameliorate agitation and disinhibited behavior as well as depression and manic symptoms following TBI. (Azouvi et al., 1999; Bakchine et al., 1989; Perino et al., 2001) Valproate may improve post-TBI aggressive behaviors (Wroblewski et al., 1997), episodic explosiveness (Geracioti, 1994), and bipolar syndrome. (Pope et al., 1988) Affective lability may include poorly controlled expression of mood and anxiety upset. (Arciniegas and Silver, 2001) Other agents, such as benzodiazepines may address similar symptoms, yet these drugs introduce addiction and tolerance issues and do not appear to address specific causes of affective lability.

To complicate matters clinically, the PI saw many cases in the veteran population in which TBI patients had been trying to self-treat their affectively lability—generally an irritability or anxiety state that interrupted or prevented normal functioning at work or in family life, often leading to broken marriages, job losses, occasionally to homelessness. Unfortunately, the most readily available drug of choice for many TBI victims was often ethyl alcohol. The result of self treatment was frequently the development of an alcohol use disorder that only served to worsen the fronto-limbic disinhibition following the TBI.

Alcohol abuse and/or dependence (AA/D) and mood disturbance often co-occur following TBI. (Corrigan, 1995) In a group of 20 TBI survivors who had evidence of alcohol abuse in the year following their injury, 15 (75%) developed a mood disorder. (Jorge and Robinson, 2002) In a non-alcohol abusing group, only 44% patients developed a mood disorder during the same time period. (Jorge and Robinson, 2002) In persons with AA/D and affective lability following TBI, successful treatment of mood lability may reduce or eliminate drinking behaviors.(Beresford et al., 2005) Following our interests in both alcoholism and TBI, we have accrued clinical experience in recognizing and treating patients who present with mood lability including symptoms of AA/D after TBI. We have observed a similar pattern of decrease in, or cessation of alcohol use following treatment of underlying TB I-induced affective lability. Many AA/D+TBI patients describe their emotional symptoms as contributing to their heavy alcohol

use. Observed clinically, when such cases reach alcohol abstinence, their symptoms of poorly regulated affective expression most often do not appear to be those of an idiopathic mood or anxiety disorder. They do not present the severity or the same natural courses as do Major Depressive Disorder, Bipolar Illness, or Anxiety Disorder, for example. Instead both symptoms and course appear more characteristic of the sustained affective lability often observed following TBI. (Beresford et al., 2005) This suggests that TBI survivors represent a patient group for whom treatment of neuropsychiatric symptoms following TBI may alleviate both TBI-related affective lability and also heavy ethanol use by treating the condition for which ethanol is used.

We believe our clinical observation of excessive alcohol use following TBI and the response to non-blinded, open-label treatment with anticonvulsant medications are concordant with the notion of neuronal inhibition, if noted in the absence of a clearly controlling mechanism of action. From a scientific viewpoint however, the treatment of fronto-limbic disinhibited patients has been neither blinded nor placebo-controlled to this point. As such, we can only provide an interesting observation of what appears to be a beneficial treatment response to anticonvulsant medication among patients with affective lability and AA/D following TBI. This indicates the need for a more systematic investigation of this phenomenon that, if substantiated, might improve the outcome and treatment choices for those patients who suffer from both TBI and AA/D. Further investigation requires us to focus on one agent for use in a soundly designed clinical trial. For this purpose, we have selected divalproex sodium.

Divalproex sodium is a standard and commonly used anticonvulsant and mood stabilizing agent that appears to be the best choice of active drug for the proposed study. It is a compound comprised of sodium valproate and valproic acid. In 1963, valproic acid was recognized to have anti-seizure activity, and it was approved as an anti-epileptic drug in the U.S. in 1978. The divalproex formulation, which is an enteric-coated, stable equimolar combination of sodium valproate and valproic acid, became available in 1983. In 1994, it was shown to be superior to placebo and comparable to lithium in treating acutely manic bipolar patients, and the FDA approved it in 1995 for this indication. Also, it is used in conjunction with lithium or carbamazepine to prevent recurrent manic or depressive episodes during long-term treatment of bipolar disorder (PDR, 2006).

This line of research opens an exciting area of inquiry that can 1) characterize a treatable clinical population more specifically than ever before and, 2) potentially offer an effective and widely available treatment modality that can ease the fronto-limbic disinhibition symptoms of TBI resulting in a significant lessening of ethanol intake for the same purpose. Because ethanol self-treatment often leads to increasing ethanol tolerance and the subsequent symptoms of AA/D, specific treatment for those suffering affective lability after TBI can potentially prevent AA/D in vulnerable individuals. In addition, specific treatment may also ameliorate AA/D in cases where it has already occurred. If found effective, anticonvulsant treatment for the mood and anxiety symptoms resulting from TBI offers the possibility of altering an otherwise downhill natural course into alcohol dependence, potentially affecting the many thousands of persons who suffer affective instability after closed head TBI. If proven, this treatment may act in both preventive and curative capacities. Last, establishing a treatment effect in this area will shed light on possible interactions between affective lability and neuro-inhibition as these relate to basic mechanisms whereby the brain's vulnerability to alcohol addiction becomes manifest. In short, if this study can demonstrate a valid effect it will open further doors of inquiry.

Body

Recruitment

This report closes the fifth year of study funding. As it took substantial time locally to receive all approvals for this project, we began enrollment near the end of the first year. For our initial efforts we targeted services and clinics at the Denver VA Medical Center (DVAMC) who regularly saw TBI patients. Dr. Beresford and Mr. Schmidt have made outreach presentations to the Substance Abuse Treatment Program (SATP), Mental Illness Research, Education and Clinical Center (MIRECC), Inpatient Psychiatry, Outpatient Mental Health Clinic, TBI Clinic personnel and others. We have continued generalized outreach, advertising the study throughout the DVAMC with flyers and brochures. We consented our first participant in October 2009. This was followed by the first subject to be randomized to the study drug trial in February 2010. Since then we have expanded our outreach beyond the DVAMC by running advertisements in local newspapers, public transit and more recently, television. The television ads provided a significant boost to recruitment and have propelled us to within three subjects of completion.

The past year has seen us complete study enrollment and randomization. As of June 9, 2014 we reached our goal of 50 patients randomized into the drug trial from a population of 637 potential candidates, of whom 101 were evaluated for study entry in person. See Figure 1 on subject flow and Figure 2 on the course of randomized study subject accrual over time. We have collected usable data from all 50 subjects randomized and a total of 37 (74%) have completed the protocol. Participant attendance was remarkably high, with 74% (37/50) completing the protocol once randomized, well above the anticipated 50% dropout rate.

Our staff have been hard at work and completed data entry into a comprehensive study database quickly following the completion of the final drug study participant on August 13, 2014. At same time, we are arranging for final computerized volumetric analysis of the structural MRI scans of the brain collected from the study subjects. In the coming year we plan to complete data analysis and produce a final study report. We have enlisted the expertise of Dr. Weitzenkamp of the Colorado Biostatistics Consortium for comprehensive and appropriate statistical analyses. To support this work, we have requested a No Cost Extension that will allow us sufficient time to complete the revised scope of work and provide published reports.

Key Research Accomplishments

As Dr. Beresford noted in his presentation to the Substance Abuse IPR, sponsored by the MOMRP on September 23 in Frederick, Maryland, we are very excited to report what appears to be a positive effect in the valproic acid treated group over the placebo treated group. This is based on a first analysis of group score averages. The average scores on the Agitated Behavior Scale, as reported by indentified significant others (SO) in the subjects' lives, were both statistically ($p<0.03$) and clinically significant. This means that, based on these very preliminary data, the target symptom of affective lability improved with the study treatment. We believe that the SO data is firm since it is the best measure of what subjects do rather than what they say. The alcohol use data are less clear at this point and await further, more specific analysis. So too

will construction of the data to characterize the study population more specifically. We are excited to continue to assess the outcome data from this long effort.

Reportable Outcomes

While preliminary, the above outcome is reportable. Our current plan is to subject the data to more rigorous analysis in order to verify and extend the preliminary conclusion along with others targeted in the study plan.

Conclusion

Any primary conclusions from the blinded study will occur after continued data collection and analysis have been completed now having unblended the study. We will continue to formulate and explore new questions and hypotheses from the study data.

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Appendix

Figure 1:

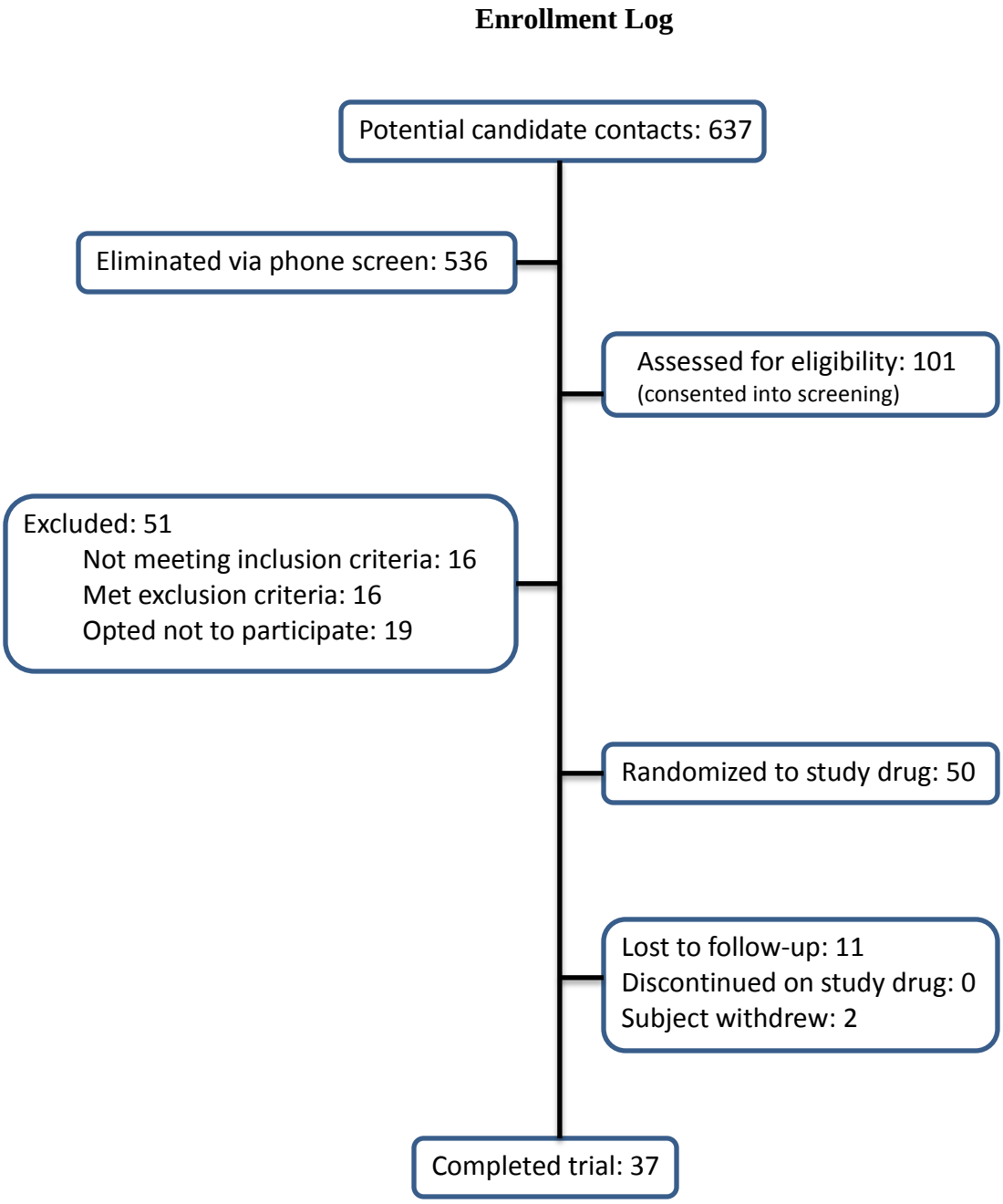

Figure 2:

Participants Randomized